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Acoustic pressure amplitude thresholds for rectified diffusion in gaseous microbubbles in biological tissue

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One of the mechanisms often suggested for the biological action of ultrasonic beams irradiating human tissues is concerned with the presence in the tissues of minute gaseous bubbles which may, under the influence of the ultrasonic field be stimulated to grow to a size at which resonance or collapse occurs with severe associated shear stresses. The evidence for the existence of microbubbles in tissues is reviewed. The results of calculations, using two existing theoretical models, of the peak pressure threshold as a function of frequency are presented. The frequency is normalized with the resonant frequency of the bubble, and results are presented for three bubble radii (1, 2, and $3.5\ \mu\text{m}$) and for different values of the gas concentration in the tissue between 0.1 and 1. The results from two models differ suggesting that an improved model and better experimental data for the threshold calculations would be appropriate for further calculations. The thresholds calculated range below the peak pressure amplitudes used in continuous wave diagnostic instruments, indicating the need for a more careful investigation both of this damage mechanism and of the exposures used in routine diagnosis. The results of calculations for typical (transient) exposure conditions from pulse-echo equipment are presented, indicating that rectified diffusion and stable cavitation are improbable phenomena in these circumstances.

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INTRODUCTION

Consideration of the irreversible effects produced when a biological system is irradiated by ultrasound is of importance both for discussion of the safety level of diagnostic applications of ultrasound, and of the potential use of ultrasound as a therapeutic agent. The details of the biological effects produced when living organisms, including human tissue, are irradiated by ultrasound, and the physical mechanisms that are involved have been recently reviewed by Reid and Sikov¹ and by Wells.² The identified mechanisms are those associated with the heating which results from the absorption by the tissue of energy from the ultrasonic wave (thermal effects), and those associated with the presence, growth, resonance, and collapse of vaporous cavities (bubbles) in the tissue (cavitation effects).

There appear to be additional effects which are observed when experiments are performed in such a way as to minimize the possibility of heating or cavitation occurring (nonthermal, noncavitation effects). Whereas it is relatively easy to monitor the prevention of thermal effects, the detection of cavitation cannot be achieved by measurement of a direct unique parameter, but relies on indirect effects.³ It is thus more difficult to be confident that no cavitation effects have been produced with a given irradiation procedure.⁴

Cavitation phenomena in liquids have been reviewed in detail by Flynn⁵ and it is well known that the threshold for the onset of cavitation depends on frequency, pulse length, temperature, pressure, viscosity, and the amount of gas dissolved in the liquid.

The work described in the present paper is concerned with the calculation of the thresholds (in terms of peak acoustic pressure) of the incident ultrasonic wave at

which stable cavitation may be induced and rectified diffusion may begin.

I. THE PRESENCE AND STABILIZATION OF GAS NUCLEI IN LIVING TISSUES

While transient and stable cavitation in biological systems have been the subject of an immense number of reports,⁶⁻²⁵ only relatively few works have given evidence of the existence of stable gas nuclei in living tissue.

Gas volumes have been observed in plant tissues by Harvey and Loomis,²⁰ Harvey *et al.*,²⁶ Nyborg *et al.*,²¹ Gershoy *et al.*,²² and Miller.^{23,25} The verification of their existence in optically opaque mammalian tissue is a more difficult problem, although investigations of decompression sickness provide evidence that gas nuclei at least are present in tissues.

Harvey and his associates have reported²⁷ a comprehensive histological study of bubble formation in animals post mortem. The animals had died as a result of decompression sickness and bubbles were found within the vascular system (in blood vessels), extravascularly (especially in fatty tissues) and also within cells and other fluid-filled spaces. Rubissow and McKay²⁸ have confirmed the existence of the bubbles in human tissue during decompression. With a frequency of 7.5 MHz they were able, on a pulsed scanning system to detect bubbles from $0.5\text{--}5\ \mu\text{m}$ in diameter. Gramiak and Shah²⁹ have reported echoes from blood passing through the human heart, some of which they ascribed to tiny gas bubbles. A number of hypotheses for the generation and stabilization of gas nuclei have been proposed.^{27,30-38} Crum³⁸ demonstrated that a Harvey-type model can lead to accurate prediction of the cavitation threshold in water. A fairly comprehensive review of stabilization mechanisms for gas-cavitation nuclei was

recently given by Yount,³⁸ who also suggested a novel model for stabilizing gas nuclei, based on surface active skins of varying permeability.

II. THE BUBBLE MODEL

Under the influence of an ultrasonic wave, gaseous bubbles in biological tissue may begin to oscillate. This oscillation may introduce significant stresses in the vicinity of the bubbles and, at a certain displacement amplitude of the bubble surface, may result in biological effects. It is therefore essential to assess the levels of displacement amplitudes which may be potentially harmful.

The amplitude of displacement of the bubble wall depends on the bubble radius and the ultrasound frequencies employed. The exact size distribution of the microbubbles in a biological system is as yet unknown. However, the existing experimental evidence indicates that the bubble sizes are most probably in the range from 0.1–5 μm .²⁸ The dimensions of the human capillary system—of the order of 3 μm are not inconsistent with this assumption. Also the scanning electron microscopic views of the endothelial cellular lining of human cord veins, recently presented by Baier,³⁹ provide strong arguments that the bubble radii are of the order of microns. These micrographic views show endothelial cells of dimensions 20 \times 5 μm with gaps between adjacent cells of the order of microns. These gaps could easily become the sites of the growth of the minute bubbles, as suggested by Harvey.²⁷

In the calculations of the acoustic pressure-amplitude thresholds for rectified diffusion reported in Sec. III, the bubble model considered is largely based on the one used by Lauterborn.⁴⁰ However, an additional comment on the present choice of the value of the polytropic exponent γ may be useful. Details of the composition of the gas contained within the bubble are not known, but it probably consists of a mixture of N_2 , O_2 , CO_2 , and H_2O vapor. The compression process of the gas in the bubble can therefore be described by a polytropic gas law. The polytropic exponent γ was chosen on the basis of the results reported by Chapman and Plesset.⁴¹ They demonstrated that the polytropic exponent γ for resonant bubbles varies between $\gamma = 1$ (isothermal oscillations) and $\gamma = 1.4$ (adiabatic oscillations), Fig. 1. For the case of the mixture of CO_2 and H_2O vapor the polytropic exponent varies between $\gamma = 1$ (isothermal oscillations) and $\gamma = 1.33$ (adiabatic oscillations). As can be seen from

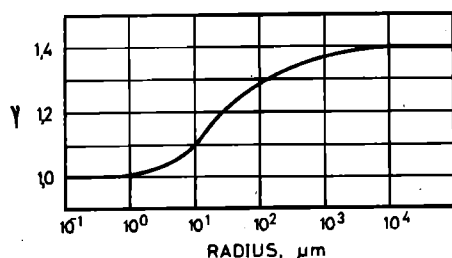


FIG. 1. The effective value of the polytropic exponent γ as a function of the equilibrium radius R_0 , after Chapman and Plesset.⁴¹

Fig. 1, the bubble oscillations are adiabatic for $R_0 = 10^{-2}$ m and isothermal for $R_0 = 10^{-6}$ m. Since the bubble radii considered (1–3.5 μm) correspond to $\gamma = 1.03$ this value of the polytropic exponent was used in the calculations. The most vigorous motion of the bubble—and hence the greatest influence on the biological system—can be expected for the bubbles of or close to the resonant size for the frequencies used. Most common clinical devices operate in the frequency range from 1–4 MHz.²

Thus from the analysis of Lauterborn,⁴⁰ the following expression may be used to calculate the relevant range of radii of bubbles resonant in this frequency range

$$f_0 = \frac{1}{2\pi R_0 (\rho_l)^{1/2}} \left[3\gamma \left(P_0 + \frac{2\sigma}{R_0} \right) - \frac{2\sigma}{R_0} - \frac{4\eta_l^2}{\rho_l R_0^2} \right]^{1/2}, \quad (1)$$

where f_0 is the resonant bubble frequency, R_0 is the resonant radius, P_0 is the ambient pressure, γ is the polytropic exponent of the gas, σ , ρ_l , and η_l are, respectively, the surface tension, the density, and the shear viscosity of the liquid surrounding the bubble.

Taking values of $\gamma = 1.03$; $P_0 = 10^5$ Pa and $\eta_l = 0.003$ Pa·s, $\rho_l = 1056$ kg·m⁻³, $\sigma = 0.06$ Nm⁻¹ (Ref. 42) which are appropriate for blood, the relationship between f_0 and R_0 shown in Fig. 2 can be calculated. It can be seen that the frequencies appropriate to the frequencies of common diagnostic use correspond to bubble radii between approximately 1.0 and 3.5 μm . The evidence of the previous section suggests not only that bubbles of these sizes may normally exist in tissue, but also that slightly smaller bubbles may exist.

Moreover, it is possible that the bubbles under the influence of the ultrasonic field may be induced to grow to their resonant size by a process of rectified diffusion. Since it may be expected that an increased number of pulsating resonant bubbles (stable cavitation) will result

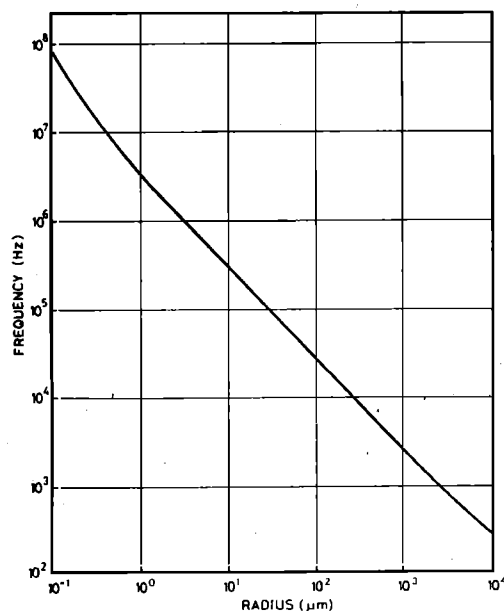


FIG. 2. Resonance frequency f_0 [calculated according to Eq. (1)] as a function of bubble radius R for a gaseous bubble in blood.

in reinforced biological effect, it is important to attempt to identify the acoustic conditions under which rectified diffusion may be induced. It is here appropriate to note that Eq. (1) is valid for a free bubble. It is recognized that the tiny gas bodies existing within the tissue may have arbitrary shapes and that their motion may be restricted due to the surrounding cells. From the recent analysis of Miller,²⁵ who derived a modified expression for calculation of the resonance frequency of the gas volumes to account for the deviation of the bubble from its spherical shape and for motion restriction it appears that this modified expression will only lead to resonance frequency somewhat different from that obtained from Eq. (1). This difference has a negligible effect on the present work calculation.

III. ACOUSTIC THRESHOLDS FOR THE OCCURRENCE OF RECTIFIED DIFFUSION

Two mechanisms (which may be related) have been suggested for rectified diffusion in the presence of an ultrasonic field. The simplest argument is that during the half-period of rarefaction (decreased pressure), the concentration of the gas within the bubble increases as gas diffuses into it, while during the compression phase gas diffuses out of the bubble. Since the amount of gas diffused is proportional to the area of the bubble, more gas will diffuse in during rarefaction than diffuses out in compression, thus causing the bubble to grow. The more sophisticated discussion of Eller and Flynn,⁴³ uses the fact that the rate of diffusion of gas in the liquid is proportional to the gradient of the concentration of dissolved gas. When the bubble contracts the thickness of a spherical shell of liquid surrounding the bubble increases, and since this reduces the concentration gradient of gas in the liquid, the rate of diffusion of gas towards the bubble increases, and the bubble will thus grow.

The mathematical theory describing the process of rectified diffusion has been given in detail by Hsieh and Plesset⁴⁴ and by Eller and Flynn.⁴³ Safar⁴⁵ has pursued the theory of Hsieh and Plesset and has obtained an expression for the acoustic peak threshold pressure amplitude required for rectified diffusion, taking account of dissipating effects

$$P_t = \rho_l \omega_0^2 R_0^2 \left\{ \left[1 - \left(\frac{\omega_A}{\omega_0} \right)^2 \right]^2 + b^2 \left(\frac{\omega_A}{\omega_0} \right)^2 \right\}^{1/2} \times \frac{(1 - c_t/c_0 + 2\sigma/R_0 P_0)^{1/2}}{[6(1 + 2\sigma/R_0 P_0)]^{1/2}}, \quad (2)$$

where P_t is the peak threshold pressure amplitude; ρ_l is the density of the liquid; $\omega_0 = 2\pi f_0$; f_0 is the linear resonant frequency of the bubble; [Eq. (1)], (Fig. 2); $\omega_A = 2\pi f_A$; f_A is the ultrasound frequency; R_0 is the equilibrium radius of the bubble; c_t is the initial uniform concentration of gas in the liquid with the bubble absent, and also the concentration at an infinite distance from the center when the bubble is present; c_0 is the saturation concentration at a pressure of P_0 ; P_0 is the hydrostatic pressure in the liquid; σ is the surface tension coefficient; and b is the total linear dimensionless damping constant consisting of radiation, thermal, and

viscous components.⁴⁶

An expression for the acoustic peak threshold pressure amplitude for rectified diffusion has also been given by Eller⁴⁷:

$$P_t = \frac{P_0}{\epsilon} \left| \frac{1 + 2\sigma/R_0 P_0 - c_t/c_0}{(3 + 4K)(c_t/c_0) - (1 + 2\sigma/R_0 P_0)K} \right|^{1/2}, \quad (3)$$

where

$$\frac{1}{\epsilon} = \frac{\rho_l R_0^2}{P_0} [(\omega_0^2 - \omega_A^2)^2 + (\omega_A \omega_0 b)^2]^{1/2}$$

and

$$K = \frac{1 - \rho_l \omega_A^2 R_0^2 P_0 + 5\sigma/3P_0 R_0}{1 + 4\sigma/3P_0 R_0}.$$

Equations (2) and (3) are both based upon the same physical model. The fundamental assumption in each case is that mass transport in the liquid is governed by a diffusion equation with spherical symmetry. Both expressions are valid for small pressure amplitudes and have been derived for continuous wave pressure fields. The main difference between the two expressions is a correction factor K introduced by Eller⁴⁷ to account for the possible nonlinear character of the assumed radial pulsation of the bubble.

Equations (3) and (4) have been used to calculate the thresholds of acoustic pressure at which rectified diffusion may be induced for different relative concentration (c_t/c_0) of dissolved gas, and different relative frequencies f_A/f_0 , see Figs. 3 and 4. (f_0 is the linear resonant frequency of the bubble—see Eq. (1) and Fig. 2—and f_A is the frequency of the continuous-wave ultrasonic field applied.) The thresholds calculated are plotted in Figs. 3 and 4. The calculations were performed using the values of liquid properties appropriate for blood (see Sec. II) at atmospheric pressure ($P_0 = 10^5$ Pa) and for equilibrium bubble radii (R_0) of 1, 2, and 3.5 μm .

Note that for a bubble radius of 3.5 μm $f_A/f_0 = 1$ corresponds to acoustic frequency f_A of 1 MHz. Likewise for a bubble radius of 2 μm , $f_A/f_0 = 1$ corresponds to acoustic frequency f_A of about 2 MHz and finally for a bubble radius of 1 μm , $f_A/f_0 = 1$ corresponds to acoustic frequency of 4 MHz (cf. Fig. 2). According to Devin⁴⁶ and Prosperetti⁴⁸ the linear damping constant b for small resonant bubbles considered here is dominated by the viscous component b_v . The resonance value of this viscous component was calculated from the expression;

$$b_v = 4\eta_l/\omega_0 \rho_l R_0^2, \quad (4)$$

where η_l is the coefficient of shear viscosity in the medium. It should be mentioned that Eller⁴⁹ extended results obtained by Devin⁴⁶ for the damping constants of resonant bubbles to the off-resonance case and pointed out that thermal damping is important for bubbles driven below resonance and that radiation damping is important for those above resonance. However, calculations show that for the range of conditions considered here viscous losses prevail. Inspection of the graphs, Figs. 3 and 4, shows that P_t increases as the gas concentra-

tion in the liquid decreases. On the other hand P_t decreases as the frequency of the applied sound field approaches the resonant frequency of the bubble.

Although, as previously mentioned, the values of damping constant calculated according to Eq. (4) are valid for frequency equal to, or very close to the resonance frequency of the bubble, the rectified diffusion thresholds were also plotted for f_A/f_0 values well below the resonance. This was done to demonstrate, within the restriction on the validity of the analysis applied, and mentioned above, the expected general tendency that the lowest threshold will appear for the bubble of or close to the resonant size for the frequencies used. Further comparison of the figures reveals rather large discrepancies in the predicted thresholds, depending on the equation used for the calculation. While Safar's expression [Eq. (2)] results in the lower (i.e., worst) resonant rectified diffusion thresholds (approximately 0.8×10^5 Pa, 0.3×10^5 Pa and 0.1×10^5 Pa for bubbles of 1, 2, and $3.5 \mu\text{m}$, respectively), Eller's equation [Eq. (3)] yields higher values.

Equations (2) and (3) have been experimentally confirmed at frequencies of 11 (Ref. 50), 22 (Ref. 51), and 28 kHz.⁴⁷ At these frequencies, depending on the bubble

radii, given parameter set and the equation used for the calculation, a reasonable agreement (i.e., to within 20%–30%) between the predicted and the measured values of P_t was obtained. However, these frequencies are well below the range of frequencies considered here. The only experimentally based information on threshold for rectified diffusion in water for bubbles resonant in the low megahertz range seems to be that presented by Miller.⁵² He obtained an approximate agreement with both of Eq. (2) and (3) for c_t/c_0 in the range 0.4–0.6 and experimentally determined γ of 1.2. Although Miller's experiment was performed under conditions which are not fully adequate for immediate comparison the computation results of this work are consistent with Miller's conclusion that the threshold for rectified diffusion according to Safar's equation is lower than the one obtained from Eller's expression and that both thresholds decrease with increasing c_t/c_0 . The discrepancies observed in the present calculations indicate the necessity of further work at higher frequencies for a possible modification of the expressions for P_t . It can be seen from Figs. 3

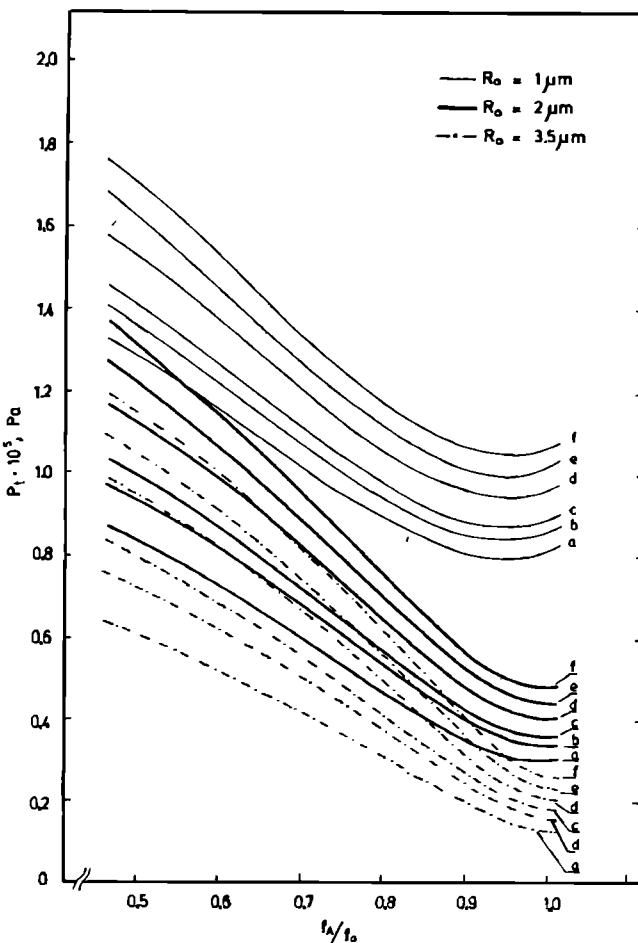


FIG. 3. Peak pressure thresholds P_t for rectified diffusion calculated according to Safar⁴⁵ [Eq. (2)] for different relative frequencies f_A/f_0 and concentrations c_t/c_0 : (a) $c_t/c_0=1$, (b) $c_t/c_0=0.85$, (c) $c_t/c_0=0.75$, (d) $c_t/c_0=0.5$, (e) $c_t/c_0=0.3$, and (f) $c_t/c_0=0.1$.

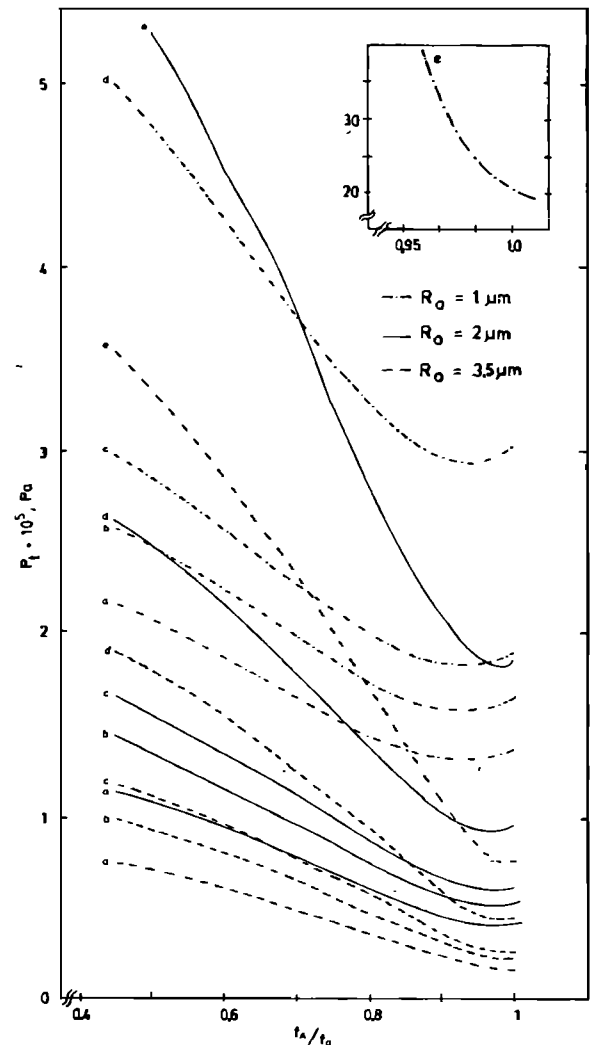


FIG. 4. Peak pressure thresholds P_t for rectified diffusion calculated according to Eller⁴⁷ for different relative frequencies f_A/f_0 and concentrations c_t/c_0 : (a) $c_t/c_0=1$; (b) $c_t/c_0=0.85$; (c) $c_t/c_0=0.75$; (d) $c_t/c_0=0.5$; (e) $c_t/c_0=0.3$.

and 4 that the expressions predict the lowest thresholds at frequencies which deviate slightly from the linear resonant frequencies f_0 (Fig. 2). The reason for this can be traced to the correction factor

$$\{[1 - (\omega_A/\omega_0)^2]^2 + b^2(\omega_A/\omega_0)^2\}^{1/2}$$

in Eqs. (2) and (3) which reaches a minimum value for ω_A/ω_0 slightly lower than unity.

It can also be seen that Eller's equation [Eq. (3)] is highly dependent on the parameter c_l/c_0 —the concentration of gas in the surrounding liquid—and ceases to be valid for $c_l/c_0 < 0.1$ as the expression under the square-root sign becomes negative. For c_l/c_0 in the range 0.3–1.0, the difference between the thresholds given by Eqs. (2) and (3) increases with decreasing c_l/c_0 .

The authors are not, for the time being, able to give a plausible explanation on the discrepancies observed in the present calculations. Therefore, to avoid a prospective confusion, the above-emphasized approximate nature of the equations used for the calculation should be kept in mind whenever employing Safar and Eller's expression for rectified diffusion thresholds calculations. Furthermore, as pointed out previously, it should be remembered that the calculation is based on the analysis that assumes a free bubble and may not be fully applicable in the clinical situation. Miller's²⁴ modified expression for calculation of the resonance frequency of the gas volumes accounting for the deviation of the bubble from its spherical shape and motion restriction indicate that his expression leads to a slightly different value of the resonance frequency when compared to the f_0 calculated from Eq. (1). This effect may be neglected from the point of view of the present analysis. However, in the clinical situation, it is most likely that the bubbles are trapped in the cracks of the cell membranes. If this is the case, the surface area of the bubble which is directly exposed to the intercellular liquid is smaller, which in turn may have an influence on the rectified diffusion process and threshold. This influence, however, is difficult to estimate as no adequate theory describing the dynamic behavior of the bubbles in cracks so far exists.

IV. DISCUSSION

It is relevant to compare the results of the calculations presented above with the levels of exposure used in medical applications bearing in mind the above assumptions used and their associated application restrictions. Several surveys of the intensities output by different commercial diagnostic instruments have been published.^{53,54} These suggest that the maximum outputs are for pulse-echo equipments of the order of $200 \text{ W} \cdot \text{cm}^{-2}$ for durations of $10 \mu\text{s}$, and for continuous wave equipments of the order of $375 \text{ mW} \cdot \text{cm}^{-2}$ (spatial average, temporal average). The lowest thresholds for rectified diffusion from Figs. 3 and 4 are peak values of $0.1 \times 10^5 \text{ Pa}$ and $0.3 \times 10^5 \text{ Pa}$, which for plane waves, correspond to intensities of the order of $3 \text{ mW} \cdot \text{cm}^{-2}$ and $30 \text{ mW} \cdot \text{cm}^{-2}$, respectively. These are thus well below the intensities used by both pulsed and continuous

wave devices, and are indeed within the exposure level quoted by AIUM.⁶

Conversely, with the assumption of plane waves, the AIUM figure of $100 \text{ mW} \cdot \text{cm}^{-2}$ corresponds to approximately $0.5 \times 10^5 \text{ Pa}$. It can be seen from Figs. 3 and 4 that, whereas this will only give rise to rectified diffusion, according to Eller, for bubbles of $3.5 \mu\text{m}$ radius for gas concentrations above 0.75 (and for a gas concentration of 1— for $2 \mu\text{m}$ bubbles); according to Safar it will give rise to rectified diffusion for both $2 \mu\text{m}$ and $3.5 \mu\text{m}$ bubbles at all gas concentrations above 0.1. It is probable that if continuous wave devices are used, rectified diffusion will take place leading to an increased number of resonant bubbles at frequencies close to 1 MHz ($R_0 = 3.5 \mu\text{m}$) and 2 MHz ($R_0 = 2 \mu\text{m}$) and more significant biological effects may result. For comparison, the lowest thresholds for rectified diffusion are shown in Fig. 5 together with the maximum outputs from diagnostic devices and the summarizing biological effects graph of Wells² (which was calculated for on intensity, while the exposure time is the on time, and no frequency dependence is described by it).

It may be expected that the occurrence of rectified diffusion depends on the character of the driving sound pressure and thus depends on the mode of operation of the ultrasound device. In the pulsed mode of operation short pulses (often only $1\text{--}3 \mu\text{s}$), of repetition rate $1\text{--}3 \text{ kHz}$, are employed and the peak pressure of the pulses can readily exceed 10^5 Pa .⁵⁵ As was mentioned

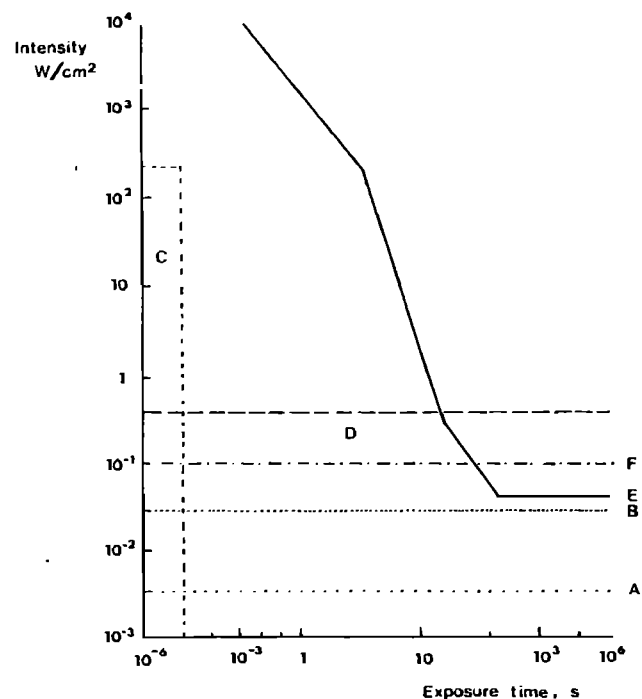


FIG. 5. A comparison of the lowest thresholds for rectified diffusion from Fig. 3 (line A) and Fig. 4 (line B) (corrected using plane-wave relationships) with data on measured outputs from diagnostic ultrasonic devices⁵³ (area C: Pulse-echo; area D: Continuous-wave), the curve of the incidence of biological effects (curve E),² and the level specified in the AIUM statement (curve F).⁶

TABLE I. Calculated decay times for oscillating resonant bubbles in blood (Ref. 56).

Bubble radius	Decay time (s)
0.5 μm	$\sim 0.44 \cdot 10^{-7}$
1 μm	$\sim 0.17 \cdot 10^{-6}$
2 μm	$\sim 0.67 \cdot 10^{-6}$
3.5 μm	$\sim 1.62 \cdot 10^{-6}$

above, the expressions of Eller and Safar are valid only for steady-state conditions and moderate pressures and thus may not be applicable to the pulsed mode of operation in which diagnostic scanners operate. As far as the authors are aware, no theory for rectified diffusion adequate for the case of pulse excitation of the bubble exists. Some information on the occurrence of rectified diffusion under these conditions has been obtained from the solution of the equation of bubble motion.⁵⁶ The computations showed⁵⁶ that the bubble returned to its equilibrium radius almost immediately after the applied sound field was switched off. The results were consistent with the theoretical values for decay times of the displacement amplitude of the oscillating resonant bubbles obtained from an analytical solution of the linearized equation of bubble motion.^{46,57} These decay times, calculated with the inclusion of loss mechanisms due to thermal, viscous dissipation, and radiation are given in Table I. The shear stresses associated with the velocity gradients in the acoustically induced flow field around the pulsating bubble influencing the bubble environment (cell membrane) will be discussed in the separate paper.⁵⁵

V. CONCLUSION

From the foregoing discussion it can be concluded not only that microbubbles are likely to exist in some living tissues (and in blood in particular), but also that resonant bubbles may be expected to play a significant role in the interaction between ultrasound and biological tissue. In the fields generated by currently available diagnostic devices operating in the continuous wave mode, the bubbles may, by a process of rectified diffusion, grow into resonant bubbles in the size range 2–3.5 μm .

The discrepancy between the results from the two theoretical expressions used indicates that a more sophisticated theoretical development may be needed. However, it is relevant to mention the other prerequisites for a reliable identification of the conditions of the inception of this mode of biological action, which are, for a given tissue, evidence of the existence of microbubbles, reliable values for the parameters used in the formula (i.e., density, surface tension, viscosity, polytropic exponent of the gas, damping coefficient), and some measurement of the type and concentration of gas in the tissue. The potential difficulty of achieving all these steps should not, in the authors' opinion, be a discouragement to the pursuance of work in this important area.

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